

IN THE SPECIFICATION:

After the title on page 1, please replace the following paragraph:

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This application is a continuation of U.S. Application Serial No. 09/171,845, filed on October 28, 1998, now U.S. Patent No. 6,335,199, which is a national stage filing under 35 U.S.C. § 371 of International Application No. PCT/FR98/00389, filed on February 27, 1998, which International Application was not published by the International Bureau in English on September 3, 1998.

Please replace the paragraph beginning on Page 1, line 15 with the following:

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The transfer of a gene into a given cell is the very basis of gene therapy. This new technology, whose field of application is vast, makes it possible to envisage the treatment of serious diseases for which the conventional therapeutic alternatives are not very effective, or are even non-existent, and applies to diseases which are either of genetic origin (hemophilia, cystic fibrosis, myopathy and the like) or acquired (cancer, AIDS and the like).

Please replace the paragraph beginning on Page 2, line 26 and ending on Page 3, line 34 with the following:

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Several nonviral methods are currently available. By way of example, there may be mentioned coprecipitation with calcium phosphate, the use of receptors mimicking viral systems (for a review see Cotten and Wagner, 1993, Current Opinion in Biotechnology, 4, 705-710), or the use of polymers such as polyamidoamine (Haensler and Szoka, 1993, Bioconjugate Chem., 4, 372-379) or of polymer such as those presented in WO 95/24221 describing the use of dendritic polymers, the document WO 96/02655 describing the use of polyethyleneimine, or of polypropyleneimine and the documents US-A-5,595,897 and FR 2,719,316 describing the use of conjugates of polylysine. Other non-viral techniques are based on the use of liposomes whose value as agent allowing the introduction, into cells, of certain biological macromolecules, such as for example DNA, RNA, proteins or certain pharmaceutically active substances, has been widely described in the literature. To this end, several teams have already proposed the use of cationic lipids which have a high affinity for cell membranes and/or nucleic acids. Indeed, although it has been shown, in the case of nucleic acids, that this type of macromolecule is capable of crossing the plasma membrane of some cells *in vivo* (WO 90/11092), it is nevertheless the case that the observed transfection efficiency is still highly limited, because of in particular the polyanionic nature of the nucleic acids which prevent their passage across the cell membrane, which itself has a negative net apparent charge. Since 1989 (Felgner et al., Nature, 337, 387-388), cationic lipids have been presented as molecules which are

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advantageous for promoting the introduction of large anionic molecules, such as nucleic acids, into certain cells. These cationic lipids are capable of complexing anionic molecules, thus tending to neutralize the negative charges on said molecules and to promote their coming close to the cells. many teams have already developed various cationic lipids. By way of example, there may be mentioned DOTMA (Felgner et al., 1987, PNAS, 84, 7413-6417), DOGS or Transfectam™ (Behr et al., 1989, PNAS, 86, 6982-6986), DMRIE and DORIE (Felgner et al., 1993, Methods 5, 67-75), DC-CHOL (Gao and Huang, 1991, BBRC, 179, 280-285), DOTAP™ (McLachlan et al., 1995, Gene Therapy, 2,674-622) or Lipofectamine™, as well as those described in Patent Applications WO9116024 or WO9514651.

Please replace the paragraph beginning on Page 10 with the following:

C⁴
Such conjugates can be easily obtained by techniques widely described in the literature, and more particularly by chemical coupling, in particular using protecting groups such as trifluoroacetyl or Fmoc or Boc; onto the polyamine and more particularly using one or more orthogonal protecting groups such as those described in Protective Groups in Organic Synthesis (p. 309-406, 1991, eds. T.W. Greene, P.G.M. Wuts, Wiley) onto the polyamine or the diaminocarboxylic acid. The selective deprotection of a protecting group then makes it possible to couple the targeting component, and the lipid is

CH
then deprotected. It should be stated, however, that the substitution of the nonreactive groups such as the carbon atoms in the CH or CH₂ groups will be carried out during synthesis of the compounds of the invention by methods known to a person skilled in the art, whereas the reactive groups, such as the primary or secondary amines, may be the subject of substitutions on the neosynthesized lipids of the invention.

Please replace the paragraph beginning on Page 14, line 27 with the following:

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The invention also relates to a process for preparing the complexes of cationic compounds/anionic active substances, said process being characterized in that one or more lipids in cationic form or a composition according to the invention whose lipid is in cationic form are brought into contact with one or more active substances comprising at least one negative charge and in that said complex is recovered, optionally after a purification step. It also relates to the kits for preparing such complexes comprising one or more lipids or one or more compositions according to the invention.

Please replace the paragraph beginning on Page 16, line 11 with the following:

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In the case of the second variant, subsequent dialysis may optionally be carried out in order to reduce the detergent and to recover the complexes. The principle of such a

C⁶ method is for example described by Hofland et al. (1996, PNAS 93, p 7305-7309) and in chapter II of the Philippot et al. document (G. Gregoriadis, 81-89, CRC Press 1993).

Please replace the paragraph beginning on Page 18, line 1 with the following:

C⁷ The complexes according to the invention can be used as a medicament for curative, preventative or vaccinal purposes. Accordingly, the subject of the invention is also the complexes of the invention as a medicament for curative, preventive or vaccinal purposes. Such complexes may be used in a method of therapeutic treatment which consists in transferring at least one therapeutically active substance, in particular a polynucleotide, into target cells, in particular a mammalian cell, and more precisely a muscle cell, a hematopoietic stem cell or, a cell of the airways, more particularly a tracheal or pulmonary cell or, a cell of the respiratory epithelium.

Please replace the paragraph beginning on Page 19, line ²⁰~~10~~ with the following:

C⁸ The complexes according to the invention may be administered by the intramuscular, intratracheal, intranasal, intracerebral, intrapleural, intratumoral, intracardiac, intragastric, intraperitoneal, epidermal, intravenous or intraarterial route by a syringe or by any other equivalent means, systems suitable for the treatment of the airways or of the mucous membranes such as inhalation, instillation or aerosolization. There may

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also be mentioned the modes of administration by application of a cream, by oral administration or any other means known to the person skilled in the art and applicable to the present invention.

Please replace the paragraph beginning on Page 19, line 32 and ending on Page 20, line 2 with the following:

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It is also within the scope of the invention to target specific organism or tissues by administration, in particular by the intravenous route, of a complex according to the invention prepared as to adjust the ration of the compound or composition/therapeutically to the active substance in said complex, the apparent charge of the complex (see in particular Liu et al., 1997, Gene therapy, 4, 517-523; Thierry et al., 1995, P.N.A.S., 92, 9742-9746).

Please replace the paragraph beginning on Page 21, line 20 with the following:

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The examples below illustrate the invention without limiting it in any manner.

Please insert the following on Page 21, after line 26:

BRIEF DESCRIPTION OF THE FIGURES

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Figure 1. A diagram of the synthesis of a cationic lipid having the formula I.

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Figure 2. Luciferase activity obtained *in vivo* after intravenous injection of a complex of the present invention, containing the lipid pcTG337, in the presence or absence of DOPE, and a plasmid containing the gene for luciferase pTG11o33.

Please replace the paragraph beginning on page 24, lines 16-17 with the following:

- C¹²
1. Preparation of the lipid pcTG37 (and optionally DOPE)/DNA complexes.

Please replace the paragraph beginning on page 26, lines 1-2 with the following:

- C¹³
2. Preparation of the complexes lipid pcTG39 (and optionally DOPE)/DNA complexes.

Please replace the paragraph beginning on page 26, lines 7-8 with the following:

- C¹⁴
1. Preparation of the lipid pcTG37 (and optionally DOPE)/DNA complexes.

Please replace the paragraph beginning on Page 27, lines 1-2 with the following:

- C¹⁵
2. Preparation of the complexes lipid pcTG39 (and optionally DOPE)/DNA complexes.

Please replace the paragraph beginning on Page 28 line 9 with the following:

C14
The analyses are carried out on a Coulter N4Plus (Coultronics France S.A.,
Margency, France) at 25°C after equilibration of the sample for 20 min. An aliquot of the
sample is aspirated and discharged several times before being pipetted. The sample is
diluted in the measuring tank and homogenized. The measurement of the light diffracted at
90° is carried out for 180 sec after a 180 sec wait. The range used goes from 3 nm to 10
000 nm using 31 bins. To be valid, the sample should give between 50,000 and 1,000,000
counts/sec.